RESEARCH ARTICLE

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Potential of Corncob Extract on the Expression of *Ki-67* and *Caspase3* in Breast Cancer

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Abstract

Objective: The expression parameters of *ki-67* and *caspase3* in breast cancer model rats will be examined in this study to evaluate the effect of corncob extract administration on breast tissue of breast cancer animal model. **Methods:** Twenty-one female Sprague Dawley rats were induced by DMBA. The experimental group was divided into three groups, after the formation of breast cancer experimental animals, the treatment group was given corncob, and the group of rats that were given 200 mg/kg BW of corncob extract and 250 mg/kg BW. The expression of *ki-67* and *caspase3* was evaluated using the immunohistochemical method. **Results:** Corncob extract increased *Caspase-3* expression in breast cancer experimental animals but did not significantly reduce *Ki-67* expression in breast cancer in Spraque Dawley rats. **Conclusion:** Administration of corncob extract had an effect on caspase3 expression (as a marker of apoptosis) but had no effect on the expression of *ki-67* (as a marker of proliferation.

Keywords: Corncob- breast cancer- *ki-67- caspase3*

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Introduction

Every year billions of tons of agricultural production waste are generated worldwide, one of the waste generated is corncob, this is because the increase in corn production from 6 million tons to 20 million tons causes an increase in corncob waste, according to data from the Directorate General of Food Crops there are 13 billion tons of corncob waste produced in Indonesia [1]. Corncobs include Neglected farming products (NAPs) defined as waste materials in agricultural production [2]. The utilization of corncobs is still very limited [3], usually used as kitchen fuel and fumigation to repel mosquitoes [4], even though there are studies that state that corncobs have active compounds [5], corncob extract is known to contain polyphenol compounds that are anticancer. Polyphenols are a class of chemical compounds consisting of one or more hydroxyl groups (-OH) bound directly to aromatic hydrocarbon groups, which are natural bioactive molecules found in plant tissues [6].

Some of the benefits of phenolic compounds in corncob extracts have potential as antioxidants [4], the phenolic fraction of corncobs can act as a free radical scavenger [3], potentially as a singlet oxygen stabilizer and can absorb UV rays [7], it is also known that corncob extract can reduce cancer cell viability and induce cell cycle arrest in the G0/G1 phase by increasing the expression level of the cyclin dependent kinase inhibitor p21 [8] and is involved in the mechanism of changing the number of proteins in the process of breast cancer cell death so as to triggering apoptosis [2]. Previous research shows that corncobs contain phenolic compounds that can be anticancer [8]. Dong, [9] mentioned that in corncobs there is resveratrol which is a phenolic compound [9], resveratrol is a natural phenolic compound that can also be found in berry skin or grape skin which functions as a phytoalexin to protect against fungal infections [10]. Resveratrol compounds are known to suppress malignant cell growth, induce cell cycle arrest, restore apoptosis, prevent procarcinogen activation and inhibit metastasis [11]. Resveratrol supplementation in 7,12-dimethylbenz(a)anthracene (DMBA)-induced Sprague Dawley was able to reduce proliferation and decrease the number of apoptotic breast cancer cells (DMBA). number of apoptotic breast cancer cells [12]. Until now, there has been no research on the benefits of corn cobs as anticancer in reducing cancer cell proliferation and increasing apoptosis cancer cell.

Breast cancer is a localized disease, but very easy to

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metastasize [13], In 2020, there were about 2.3 million new cases of breast cancer and about 685,000 cases of death due to breast cancer, it is predicted that by 2050 the burden of breast cancer will increase to more than 3 million new cases per year (40% increase) and more than 1 million deaths per year (50% increase). Cancer causes excessive cell proliferation, uncontrolled proliferation is manifested by changes in the expression or activity of cell cycle-related proteins [14]. One of these proteins is nonhistone nuclear protein expressed in proliferating cells is ki-67 protein [15], *ki-67* expression can provide an index of cancer cell proliferation.

In addition, cancer also results in the inhibition of apoptosis [16]. Caspases are a family of protease enzymes that play an important role in apoptosis [17], and are associated with cancer progression [18]. Caspase3 is a key zymogen in cell apoptosis and is not activated until cleaved by initiator caspases [19]. If caspase3 has been activated, cell death occurs in the form of apoptosis [20]. Activation of caspase3 degrades many cellular proteins and is responsible for morphological changes and Deoxyribonucleic acid (DNA) fragmentation in cells during apoptosis [21].

With the increasing incidence of breast cancer, developing natural therapies for cancer treatment without damaging other parts of the body is the biggest challenge in designing cancer treatment therapies [22], the use of natural ingredients as drugs can be synergistic in cancer therapy in addition to considering economic benefits, and low toxicity, and can be used as a companion to the main cancer treatment in helping to destroy cancer , besides that it can also minimize the side effects of the main cancer treatment. Therefore, this study aims to determine the effect of corncob extract on breast cancer through the expression of *ki-67* and *caspase3*.

Materials and Methods

2.5 kg of corncobs from corn plantations in Mojokerto, East Java, corncobs are not attacked by pests, and are not damaged, then dried for about 1 month not exposed to direct sunlight, after drying in puree and continued the maceration process using 96% ethanol. The corncob extract produced by maceration has an organoleptic form of thick liquid, brown in color with an extract weight of 10 grams.

The animals used were female Sprague Dawley rats aged 30 - 40 days, body weight 85 - 90 grams, all animals were housed and acclimatized under optimum conditions (21 - 240C) and lighting (12-hour dark/light cycle) at the Integrated Research and Testing Institute of Gadjah Mada University experimental animal unit, during the study the animals were given appropriate food and drink ad libitium.

Sample collection

Twenty-one female Sprague Dawley rats were divided into three groups, namely K (control group), P1 (200 mg corncob extract / BW rat), P2 (250 mg corncob extract / BW rat), the number of animals tested in this study was calculated using the Lemeshow formula where based on this formula, each group consisted of seven animals. All groups of experimental animals were given DMBA as a carcinogen for 5 weeks through an intragastric sonde, then evaluated every week until there was a lump on each breast of the experimental animals by palpation, to prove breast cancer, one rat was sacrificed to see any changes in cell size or shape. After obtaining the animal model of breast cancer, only the treatment group given corncob extract

Immunohistochemistry

The expression of *ki-67* and *caspase3* was examined by immunohistochemical method using mouse monoclonal antibodies *ki-67* (ELK, Biotechnology Inc., EM-1064) and caspase3 (ELK, Biotechnology Inc., EM-1266. Wuhan, China). Examination of *ki-67* and *caspase3* expression was performed by observers on histology preparations using a standard light microscope 40x objective lens, 10x ocular lens, and *ki-67* and *caspase3* scores were defined as the average of cancer cells stained with antibodies [15]. The technique of counting *ki-67* and *caspase3* expression uses the Visual Counting Using a Microscope method where the pathologist finds 'hotspot areas', which are areas where there is an increase in tumor proliferation counted in 500 cells. Observation of histology preparations was performed using a Leica DM750 microscope at the Integrated Laboratory, Faculty of Medicine, Universitas Airlangga. Documentation was obtained using the integrated camera available at the laboratory.

Statistical analysis

The data obtained were analyzed using the IBM Statistical Program for Social Science (SPSS) Version 27 to determine differences in *ki-67* expression and *caspase3* expression after administration of corncob extract. Analysis of normality data resulted in a normal distribution of data, so continued with One way ANOVA.

Results

Data analysis

To determine the difference in *Ki-67* expression and Caspase3 expression after the administration of corncob extract using data analysis with the IBM Statistical Program for Social Science (SPSS) version 27 application on *ki-67* and *caspase43* expression levels by analyzing the mean and standard deviation in all groups. For numerical data, a normality test is carried out, the data obtained is normally distributed ($p > 0.05$), then proceed with the homogeneity test using the Levene test, the data obtained is homogeneous because the significance value obtained is $p \geq 0.05$, because the results of these tests are normally distributed data ($p > 0.05$) and all data variations are homogeneous ($p > 0.05$), so it can be continued with parametric comparative tests.

Expression of Ki-67

To ensure the quality of the research, it was ensured that the reagents used did not expire. The treatment of corncob extract administration in the 200 mg and 250 mg treatment groups in this study began with observing the results of HE staining, in sacrificed test animals to ensure that cancer cells had formed in the breasts of Sprague

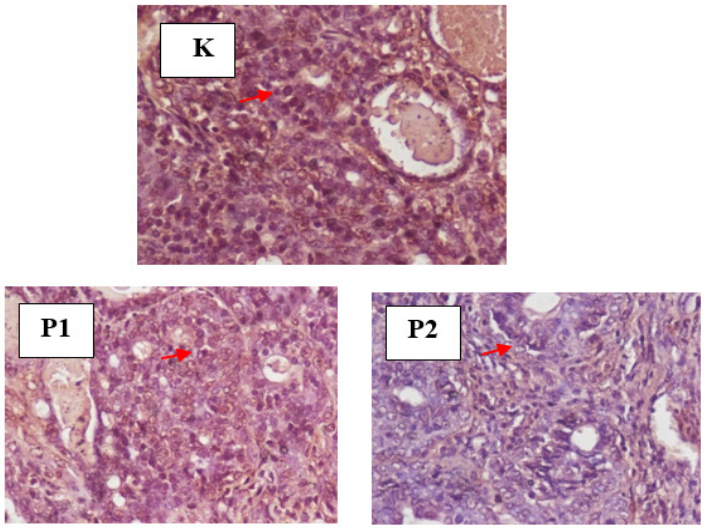

Figure 1. Microscopic Examination of *ki67* Antigen. Note: Control group (K) and treatment group after administration of exctract corncob (P1) 200 mg (P2) 250 mg. The brown spots indicate a binding to the anti-Ki-67 monoclonal antibody and the chromogen Diaminobenzidine (DAB) (bred arrow)

Dawley rats induced with DMBA.

Histopathology preparation (HPA) with immunohistochemical staining method of Sprague Dawley breast cancer cells. In Figure 1, it can be seen that there is a increased expression of *ki-67* both in the control group and the treatment group with the administration of corncob extract (P1 = 200mg; P2 = 250 mg). Positive expression of *ki-67* is indicated by brown spots (black arrows) which is an immuno-reaction between *ki-67* antigen in epithelial tissue that binds to anti *ki-67* monoclonal antibody (ELK Wuhan Biotechnology CO,. LTD., China PR), HRP secondary antibody and diaminobenzidine (DAB) substrate.

The ANOVA test results showed that there was no significant difference in the mean *ki-67* expression of all groups ($p > 0.01$). The mean *ki-67* expression levels shows that the administration of corncob extract in the treatment group did not significantly reduce Ki-67 expression compared to the control group.

Expression of caspase3

Histopathology preparation (HPA) with immunohistochemical staining method of breast cancer cells that have been transformed In Figure 2, it can be seen that there is a positive caspase3 expression in both the control group and the treatment group with the administration of corncob extract (P1 = 200mg; P2 = 250 mg). Positive caspase3 expression is characterized by brown spots (black arrows) which is an immuno-reaction between caspase3 antigen in epithelial tissue that binds to caspase3 monoclonal antibody (ELK Wuhan Biotechnology CO,. LTD., China PR), HRP secondary antibody and diaminobenzidine (DAB) substrate.

ANOVA results show that there is a significant

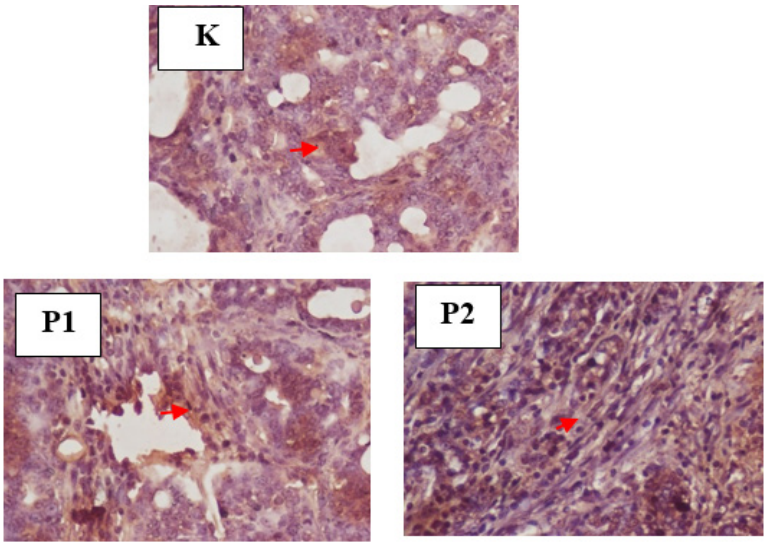

Figure 2. Microscopic Examination of Caspase3 Antigen. Note: Control group (K) and treatment group after administration of extract corncob (P1) 200 mg (P2) 250 mg. The brown spots indicate a binding to the anti-caspase3 monoclonal antibody and the chromogenDiaminobenzidine (DAB) (red arrow)

difference in the average expression of caspase3 from all groups ($p \leq 0.01$). The administration of corncob extract in the treatment group was able to increase the expression of caspase3 compared to the control group that was not given corncob extract which is the administration of corncob extract in group P2 (250 mg), caspase3 expression increased compared to the administration of corncob extract in group P1 (200 mg).

Discussion

Agriculture in Mojokerto district produces abundant food commodities. One of these commodities is corn, which produces a surplus of 54,000 - 156,000 tons every year. Corn post harvest old cannot be sold, but only the kernels are used as animal feed while the cobs become unusable waste. The corncobs in this study used post-harvested old corncobs because based on research the dried corncob extract has a high content of phenolic compounds, flavonoids and antioxidant activity compared to fresh corn cobs [23]. Corncob extract is obtained through the maceration method, the selection of the maceration method because it is simple, and easy to do and is carried out at room temperature so as to avoid damage to thermolabile compounds [24], there are several other factors that affect the manufacture of extracts, namely the type of solvent, the ratio of material weight to solvent volume, stirring, extraction time and sample size. Ethanol solvent is used for the process of making corncob extracts because it is relatively cheap, easy to obtain, and relatively safer than other organic solvents, the concentration of ethanol used is 96%, this is in accordance with the literature that high ethanol concentrations are better able to dissolve phenolic compounds in corncobs [4].

One of the limitations in this study is the process of making breast cancer animals models which is quite time consuming. Animal model using Sprague Dawley strain rats were chosen because they have low endurance when compared to other strains, their body size is larger and are often used as a model for cancer research that requires a rapid decrease in immunity [25], Sprague Dawley strain rats selected aged 30 - 40 days are the best induction time because the terminal end buds in the breast glands are actively proliferating, breast glands in some strains of rats are susceptible to carcinogens in inducing cancer such as Sparague Dawley, so it can be used as a good model for studying carcinogenesis, and neoplasms that form are similar to humans .

DMBA is a chemical carcinogen that is widely used to induce mammary carcinogenesis in mice [26]. The tumorigenic effect of DMBA begins by activating the arylhydrocarbon receptor (AhR), which is a DMBA ligand-activated transcription factor [27], without ligand AhR is a cytosolic protein complex, after activation by ligand binding, AHR is translocated to the nucleus, releases companion proteins and dimerizes by binding to target genes and regulating transcription of target genes, after transcriptional regulation occurs, AhR is rapidly exported to the cytosol, DMBA induction causes the AhR receptor located in the cytoplasm to act as a DMBA ligand-activated transcription factor, then translocates to the nucleus and provokes dimerization with the arylhydrocarbon receptor nuclear translocator (ARNT) [28], the AhR/ARNT complex induces gene transcription [29], encodes metabolizing enzymes CYP1A1, CYP1A2, and CYP1B1 which are Cytochrome P450 enzymes [30]. CYP1B1 converts DMBA to the active compound epoxide (DMBA-3,4 - dihydrodiol.1,2 - epoxid) or DMBA DE is a major carcinogen that is genotoxic and forms DNA adduct with the *p53* gene.

Resveratrol is a natural compound that can induce phosphorylation of *p53* at Serin15 and acetylation at Lys379, which are modifications to increase its transcriptional activity, activation by inducing phosphorylation of *p53* [31], which is the process of adding phosphate groups to proteins, can affect the activity, stability, and interaction of *p53*. Phosphorylation of *p53* is a key mechanism for regulating its function as a tumor suppressor

DREAM (downstream regulatory element antagonist modulator) is a protein complex that regulates cell cycle-dependent gene expression. *p53* regulates MKI67 expression independently of the DREAM complex by binding to *p53* responsive elements in its promoter and suppressing transcription. Resveratrol in corncob activates *p53* with a moderate level of activation due to the opposite signal, namely a positive signal from phosphorylation of *p53* by ser15. Whereas the negative signal originating from acetylation on Lys379 refers to the addition of acetyl groups to lysine residues by SIRT1 inhibiting *p53*-dependent apoptosis, consequently not enough signal to induce cell cycle arrest. resveratrol can also act as an effective SIRT1 deacetylase activator, regulating SIRT1 protein expression in interacting with *p53* and inhibiting its function through deacetylation of *p53* at the C-terminal Lys379, thereby reducing its ability to transactivate p21 target genes [31], causing a lack of gene expression p21, the lack of functionality of p21 can cause *p53* to be unable to suppress the target promoter [32] meanwhile downregulation of *ki-67* after DNA damage requires *p53* and p21 because they are co-regulatory programs to pause the cell cycle through the *p53*-p21-DREAM pathway [33], this is thought to cause cob extract does not affect the expression of *ki-67*.

Corncob induced *p53* activation does not cause cell cycle arrest or apoptosis but activated P53 is thought to stimulate autophagy, in a DRAM (damage-regulated autophagy modulator) dependent. Inactivation of cell death is a major step in tumor development, because *p53*, which is a critical mediator of cell death, and is called the guardian of the genome because of its role in responding to various external or internal pressures, often undergoes mutations [34]. P53 inactivation is a common occurrence in tumorigenesis, with mutations occurring in more than 50% of human primary tumors, when *p53* is reactivated DRAM can provide a direct link between *p53* and other pathways that control cell death [35].

DRAM is a *p53* target gene encoding a lysosomal protein that induces macroautophagy and death effector which is an important component of the *p53* apoptotic response, DRAM was first identified as a modulator of *p53*-induced autophagy, which is critical for apoptosis,

DRAM is known to induce apoptosis in many tumor cells, translocation of DRAM to mitochondria induces mitochondrial autophagy (mitophage), and can induce apoptosis [36]. DRAM induces apoptosis through AIFM1 (Apoptosis-Inducing Factor Mitochondrion-Associated 1), results in protein translocation to the nucleus which affects chromosome condensation and fragmentation, and induces mitochondria to release pro-apoptotic proteins cytochrome c and caspase-9 which in turn activates caspase3 the main implementer of apoptosis [37].

Author Contribution Statement

All authors contributed equally in this study.

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General

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Scientific Approval

This research has been approved by the chairman of the immunology study program, postgraduate faculty, airlangga university

Ethical Declaration

This study is certified to be ethically cleared by universitas airlangga, Faculty of Dental Medicine health research ethical clearance commission No 656/HRECC. FODM/VIII/.

Conflict of Interest

All authors do not have any conflict of interest.

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